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Sinonasal cancer and occupational exposures: a pooled analysis of 12 case–control studies

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Abstract

Objective: In order to examine the associations between sinonasal cancer and occupational exposures other than wood dust and leather dust, the data from 12 case–control studies conducted in seven countries were pooled and reanalyzed.
Methods: The pooled data set included 195 adenocarcinoma cases (169 men and 26 women), 432 squamous cell carcinomas (330 men and 102 women), and 3136 controls (2349 men and 787 women). Occupational exposures to formaldehyde, silica dust, textile dust, coal dust, flour dust, asbestos, and man-made vitreous fibers were assessed with a job-exposure matrix. Odds ratios (ORs) were adjusted for age, study, wood dust, and leather dust, or other occupational exposures when relevant. 95% confidence intervals (CIs) were estimated by unconditional logistic regression.
Results: A significantly increased risk of adenocarcinoma was associated with exposure to formaldehyde. The ORs for the highest level of exposure were 3.0 (CI = 1.5–5.7) among men and 6.2 (CI = 2.0–19.7) among women. An elevated risk of squamous cell carcinoma was observed among men (OR = 2.5, CI = 0.6–10.1) and women (OR = 3.5, CI = 1.2–10.5) with a high probability of exposure to formaldehyde. Exposure to textile dust was associated with non-significantly elevated risk of adenocarcinoma, among women only: the OR for the high level of cumulative exposure was 2.5 (CI = 0.7–9.0). High level of asbestos exposure was associated with a significantly increased risk of squamous cell carcinoma among men (OR = 1.6, CI = 1.1–2.3).
Conclusions: The results of this pooled analysis support the hypothesis that occupational exposure to formaldehyde increases the risk of sinonasal cancer, particularly of adenocarcinoma. They also indicate an elevated risk of adenocarcinoma among women exposed to textile dust, and suggest that exposure to asbestos may increase the risk of squamous cell carcinoma.

Introduction

Sinonasal cancer has often been related to occupational exposures. The association between exposure to wood

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dust and sinonasal adenocarcinoma is well documented [1]. Exposure to leather dust or employment in leather-related occupations has also been associated with sinonasal cancer, particularly adenocarcinoma, in several studies [2–9]. Elevated risks were observed in a number of other occupations and industries, including textile workers [3, 7, 8, 10–14], farm workers [3, 13, 15], construction workers [8, 13, 16], metal industry [3, 7, 11], workers exposed to chromium and nickel compounds [17], and to formaldehyde [18, 19]. The available results, however, are partially conflicting. Sinonasal cancer is a rare disease, with annual incidence rates around 1 per 100,000 in most countries [20], and cohort studies lack statistical power to identify excess risks. Case–control studies with complete information on occupational history included a relatively small number of cases, which precludes examining associations with specific jobs or substances. The number of cases were generally less than 100, and the largest published studies included about 200 cases [21]. Furthermore, the use of different classification systems for occupations, different definitions of exposure, and confounders, makes it difficult to summarize and interpret the findings from the different studies.

In order to improve knowledge on occupational risk factors of sinonasal cancer, a pooled analysis of 12 case–control studies on sinonasal cancer was carried out. Previous analyses from the same pooled data set examined associations with wood-dust exposure [22] and with various occupations [15]. An analysis restricted to European studies estimated attributable risks for occupation and smoking [23]. This article focuses on exposure to formaldehyde, silica, textile dust, coal dust, flour dust, asbestos, and man-made vitreous fibers (MMVF).

Material and methods

Studies

The pooled data set included 12 case–control studies from seven countries. The studies were selected on the basis of availability of information on histologic type, age, sex, smoking, and occupational histories. The studies differed according to the source of cases and controls, the method of interview, and the vital status of subjects. A more detailed description of the studies and of the inclusion criteria has been published elsewhere [15, 22, 24]. The main characteristics of the 12 studies are summarized in Table 1. On the whole the pooled data set consisted of 930 cases (680 men, 250 women), including 432 squamous cell carcinomas (330 men, 102 women) and 195 adenocarcinomas (169 men, 26 women), and 3136 controls (2349 men, 787 women). Cases were diagnosed between 1968 and 1990.

Exposure assessment

Detailed information on occupational history was collected in all studies, including the job title and years of employment for each job held. Job titles and industries were coded using the International Standard Classification of Occupations (ISCO) and the International Standard Industrial Classification (ISIC). For four studies (Biella, Vigevano, Germany, France) these codes were used by the original investigators; for four other studies (Siena, Brescia, the Netherlands, Virginia), coding was performed from the questionnaires by native speakers, while for the remaining four studies (Los Angeles, Seattle, Shanghai, Sweden) a central recoding was performed to convert the coding system originally used into ISCO/ISIC codes.

The following occupational exposures were assessed: wood dust, leather dust, formaldehyde, textile dust, flour dust, coal dust, crystalline silica, asbestos, and four types of MMVF: mineral wools (including glass wool, rock wool, and slag wool), continuous filaments, refractory ceramic fibers, and microfibers.

Exposures were assessed through a job-exposure matrix (JEM), developed specifically for this pooled analysis by four of the authors (P.A.D for wood and leather dust, E.O. for asbestos and MMVF, D.B. and M.G. for the other substances). The same criteria were adopted for all substances. Each unique combination of occupation and industry codes was assessed without knowledge of the disease status of the individual(s) who had held that job. Industrial hygiene data were used to determine semi-quantitative indices of exposure. The basis for exposure assessment was the situation in Western countries in the 1970s, but calendar periods were taken into account whenever possible (for all substances except for wood and leather dust). For each occupation/industry combination and for each substance, the JEM gives the probability of exposure (*i.e.* the proportion of exposed workers for this combination), and the level of exposure. Since the amount and quality of available industrial hygiene data varied according to the substance, different cut-off points were used for the categories of level and probability. For most of the substances the level of exposure was defined as an 8-h time-weighted-average (TWA) concentration. For asbestos and MMVF the concentration and the frequency of exposure (proportion of working time during which exposure occurred) were assessed separately. A level of exposure corresponding to an 8-h

Table 1. Description of the 12 case–control studies of sinonasal cancer included in the pooled analysis

References	Country (area)	Sex	Controls	All cases	Squamous cell carcinoma	Adeno-carcinoma	Source of cases	Source of controls	Year of interview	Year of diag-nosis, cases	Type of interview
30	China (Shanghai)	Men	269	39	18	4	Cancer registry	Resident registry	1988–1990	1988–1990	In person
		Women	145	21	6	2					
16, 26, 34	France	Men	320	167	59	82	Hospitals	Hospitals/friends	1986–1988	1986–1988	In person
		Women	89	40	18	5					
35	Germany	Men	33	33	13	3	Hospitals	Hospitals	1983–1985	1983–1985	In person
		Women	21	21	7	1					
8	Italy (Siena, Verona, Vicenza)	Men	184	55	25	13	Hospitals	Hospitals	1987–1988	1982–1987	In person or mail + telephone
		Women	70	23	8	3					
7	Italy (Brescia)	Men	70	23	12	5	Hospitals	Hospitals	1990	1980–1989	Telephone
		Women	32	11	5	1					
28	Italy (Biella)	Men	92	22	8	9	Hospitals	Hospitals	1988–1989	1976–1988	Mail + telephone
		Women	19	4	2	1					
9	Italy (Vigevano)	Men	29	16	2	11	Hospitals	Electoral rolls/ death registries	1983	1968–1982	In person
		Women	10	5	1	0					
18, 29	The Netherlands	Men	195	91	50	23	Hospitals	City registries/ death registries	1982	1978–1981	In person
36	Sweden	Men	541	44	31	3	Cancer registry	Population registries/death registries	1979	1970–1979	Mail + telephone
25, 37, 38	USA (Seattle)	Men	327	33	19	1	Cancer registry	Random digit dialing	1979–1985	1979–1983	Telephone
		Women	225	20	7	1					
Mack and Preston-Martin[a]	USA (Los Angeles)	Men	108	64	40	2	Cancer registry	Neighborhood	1979–1985	1979–1985	Telephone
		Women	70	38	15	1					
10, 39	USA (Virginia, North Carolina)	Men	181	93	53	13	Hospitals	Hospitals/death registries	1980–1982	1970–1980	Telephone
		Women	106	67	33	11					
Total		Men	2349	680	330 (48.5%)	169 (24.9%)					
		Women	787	250	102 (40.8%)	26 (10.4%)					

[a] Unpublished data.

TWA was calculated by multiplying concentration by frequency. For each substance the cut-off points for the categories of exposure indices and the quantitative values assigned to each category are presented in Table 2. When the probability of exposure was less than 10% (for wood dust and leather dust) or less than 1% (for the other substances), the job was considered as unexposed. For leather dust, because of the scarcity of data, it was not possible to make quantitative estimates corresponding to the level categories.

Several exposure variables were used to summarize the lifetime occupational exposure: the cumulative exposure (calculated as the sum of the job-specific products of probability, level and duration of exposure over the total work history), the total duration of exposure, the maximum probability of exposure, and the maximum exposure level during the working life. This article focuses on the results based on cumulative exposure, although results concerning other exposure variables are presented when they give additional information.

Table 2. Categories for level and probability of exposure defined in the JEM for the studied substances and assigned values, pooled analysis of 12 case–control studies of sinonasal cancer

	Probability of exposure		Level of exposure			
	Cut-points (%)	Assigned value	Cut-points[a]	Assigned value		
Leather dust	10–50	0.3	Low	1		
	50–90	0.7	Medium	2		
	>90	1	High	3		
Wood dust	10–50	0.3	<1	0.5		
	50–90	0.7	1–5	3		
	>90	1	>5	9		
Formaldehyde	1–10	0.05	<0.25	0.15		
	10–50	0.3	0.25–1	0.65		
	50–90	0.7	>1	3		
	>90	1				
Flour dust	1–10	0.05	<0.5	0.25		
	10–90	0.5	0.5–5	3		
	>90	1	>5	10		
Coal dust	1–10	0.05	<0.3	0.15		
	10–90	0.5	0.3–2	1.2		
	>90	1	>2	5		
Silica dust[b]	1–10	0.05	<0.01	0.005		
	10–90	0.5	0.01–0.1	0.05		
	>90	1	>0.1	0.2		
Textile dust	1–10	0.05	<0.05	0.025		
	10–90	0.5	0.05–0.5	0.25		
	>90	1	>0.5	1.5		
			Concentration[c]		Frequency[d]	
			Cut-points	Assigned value	Cut-points (%)	Assigned value
Asbestos, mineral wools, continuous filaments and ceramic fibers	1–10	0.05	<0.1	0.05	<5	0.02
	10–50	0.3	0.1–1	0.5	5–30	0.2
	50–90	0.7	1–10	5	30–70	0.5
	>90	1	>10	50	>70	0.8
Microfibers	same as asbestos			Not evaluated		

[a] In ppm for formaldehyde, in mg/m^3 for wood dust, flour dust, coal dust, silica dust, and textile dust; no quantitative estimates for leather dust (see text).
[b] Respirable dust.
[c] Concentration in fibers/ml.
[d] Proportion of working time with exposure.

Since exposure to formaldehyde and textile dust had been originally assessed in some of the 12 studies on a case-by-case basis, additional analyses were performed for these substances. The original exposure data of three studies for formaldehyde (France, the Netherlands, and Seattle) and four studies for textile dust (Shanghai, Virginia, Biella, and France) were combined and analyzed. For formaldehyde, the probability and level of exposure had been assessed in the three studies by industrial hygienists. The assignment was mainly based on job title in two of the studies (the Netherlands and Seattle). In the French study information from a specific questionnaire was also available. Three categories of exposure, comparable between the three studies, could be constructed: unexposed, possible exposure or probable exposure to low level, probable exposure to moderate or high level. For textile dust the level of exposure could not be studied, and only a dichotomous variable (exposed/unexposed) was used for the pooled analysis of the four studies. In addition, exposure to three types of textile fibers (cotton, wool, synthetics) could be assessed.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) associated with exposure to formaldehyde, silica, textile dust, coal dust, flour dust, asbestos, and MMVF were estimated using unconditional logistic regression. The cumulative exposure for each substance was categorized into four classes (unexposed and three levels according to the tertiles of the distribution among controls). Exposure categories were collapsed when the number of subjects was too small.

All ORs were adjusted for age (≤ 55, 56–65, >65) and study, and were calculated separately for men and women. Distinct analyses were performed for squamous cell carcinomas and adenocarcinomas. Other histologic types were not studied, because the classifications used were not comparable between studies.

Potential confounding factors were examined and included in the models if their inclusion changed the OR by more than 10%. Preliminary analyses showed that, although smoking was related to squamous cell carcinomas, adjustment for smoking changed the results only marginally. Therefore smoking was not included into logistic models.

For adenocarcinomas, among men, ORs were systematically adjusted for cumulative exposure to wood dust and leather dust. Some analyses were also restricted to adenocarcinoma cases and controls who had never been exposed to wood or leather dust.

Exposure lagging by 10 and 20 years was used to allow for an induction-latency period.

Heterogeneity across studies was tested by comparing logistic models with and without interaction terms between occupational exposures and studies. Study-specific ORs were examined for consistency with the pooled results. To estimate the influence of individual studies, pooled ORs were also computed successively excluding each study from the analysis. The SAS system and the BMDP software were used for data processing.

Results

Table 3 shows the ORs by gender and histologic type, associated with each of the 10 occupational exposures. A significantly increased risk of squamous cell carcinoma was associated with a high level of asbestos exposure among men. Significant excess risks of sinonasal adenocarcinoma were observed among men and women exposed to formaldehyde, among men exposed to ceramic fibers, and among women exposed to silica, textile dust, and continuous filaments.

When a 10- or 20-year induction period was taken into account, the ORs were generally slightly increased, but the results were not substantially modified. The only notable change was observed for the risk of squamous cell carcinoma associated with exposure to flour dust, among men: after lagging exposure by 20 years the ORs for low, medium, and high cumulative levels were respectively 1.2 (0.4–3.2), 1.3 (0.6–2.9), and 1.7 (0.7–4.2). The main findings in Table 3 were further investigated.

Formaldehyde

Cumulative exposure to formaldehyde was associated with a significantly increased risk of adenocarcinoma, in both sexes, and also increased slightly and non-significantly the risk of squamous cell carcinoma (Table 3). A non-significantly elevated risk of squamous cell carcinoma was also associated with a high probability of exposure to formaldehyde. Among men the OR associated with a definite exposure (probability $>$ 90%) was 2.5 (CI = 0.6–10.1). Among women no case or control had been definitely exposed to formaldehyde, but a significant three-fold increase in risk was associated with a probability of exposure greater then 50% (OR = 3.5, CI = 1.2–10.5). Among men the risk of squamous cell carcinoma was also increased after 30 years or more of exposure to formaldehyde (OR = 1.4, CI = 0.9–2.3).

All exposure variables (probability, maximum level, and duration) were associated with the risk of adenocarcinoma. However, exposure to formaldehyde was related to exposure to wood dust, a strong risk factor for

Table 3. Odds ratios of sinonasal cancer risk for cumulative exposure to occupational agents, by histologic type, and sex; pooled analysis of 12 case–control studies of sinonasal cancer

	No. of controls	Men						No. of controls	Women					
		Squamous cell carcinoma			Adenocarcinoma				Squamous cell carcinoma			Adenocarcinoma		
		No.	OR[a]	95% CI	No.	OR[b]	95% CI		No.	OR[a]	95% CI	No.	OR[a]	95% CI
Formaldehyde														
Low	265	43	1.2	0.8–1.8	6	0.7	0.3–1.9	96	6	0.6	0.2–1.4	2	0.9	0.2–4.1
Medium	266	40	1.1	0.8–1.6	31	2.4	1.3–4.5	53	7	1.3	0.6–3.2	0		–
High	211	30	1.2	0.8–1.8	91	3.0	1.5–5.7	25	6	1.5	0.6–3.8	5	6.2	2.0–19.7
Flour														
Low	31	9	2.2	1.0–4.8	0		–	65	9	0.5	0.2–1.3	2		
Medium	39	9	1.5	0.7–3.1	0	0.7	0.2–3.2	19	0		–	1	0.7	0.2–2.8
High	31	6	1.4	0.6–3.4	2			2	0		–	0		–
Coal														
Low	42	8	1.4	0.6–3.1	2			2	0		–	0		–
Medium	51	6	1.0	0.4–2.5	1	0.6	0.2–1.8	0	0		–	0		–
High	60	11	1.1	0.6–2.2	1			0	0		–	0		–
Silica														
Low	304	49	1.1	0.8–1.5	16	1.0	0.5–1.9	57	6	0.9	0.4–2.3	2	1.5	0.3–6.8
Medium	272	46	1.1	0.8–1.6	4	0.4	0.1–1.1	36	13	1.9	0.9–3.9	3	1.5	0.4–5.7
High	304	32	0.8	0.6–1.3	7	0.4	0.2–1.0	5	0		–	2	17.0	2.6–112
Textile														
Low	74	11	1.1	0.5–2.1	7	1.6	0.6–4.2	49	8	1.2	0.5–2.8	2	1.7	0.4–7.9
Medium	50	8	1.1	0.5–2.4	5	0.7	0.2–2.9	45	8	1.0	0.5–2.4	5	3.5	1.2–10.7
High	45	8	1.3	0.6–2.9	0		–	61	6	0.8	0.3–2.0	4	2.5	0.7–9.0
Asbestos[c]														
Low	351	49	1.2	0.8–1.8	17	1.4	0.6–3.2	109	11	1.1	0.5–2.3	2		
Medium	379	46	1.0	0.7–1.5	43	1.2	0.6–2.4	49	5	0.9	0.4–2.5	1	1.1	0.4–3.4
High	437	75	1.6	1.1–2.3	31	1.1	0.5–2.3	24	4	1.4	0.5–4.5	1		
Mineral wools[d]														
Low	177	14	0.5	0.3–0.9	22	1.6	0.7–3.5	18	1			1		
Medium	147	25	1.1	0.6–1.7	31	1.1	0.5–2.6	13	1	0.4	0.1–2.0	0	2.3	0.5–11.2
High	176	21	0.6	0.4–1.1	15	1.1	0.4–2.6	4	0		–	1		
Continuous filaments														
Low	33	3	0.6	0.2–2.1	1			7	2			2		
Medium	21	4	1.5	0.5–4.5	0	0.1	0.0–1.3	11	0	0.8	0.2–3.5	0	6.6	1.6–27.2
High	30	2	0.7	0.2–3.2	0			1	0		–	1		
Ceramic fibres														
Low	17	3	1.4	0.4–5.3	5	13.6	3.5–53.7	4	0		–	1		
Medium	25	0		–	2	3.5	0.7–18.5	1	0		–	0	7.1	0.7–79.0
High	23	2	0.8	0.2–3.7	1	0.9	0.1–12.6	1	0		–	0		–
Microfibres														
Exposed	35	3	1.0	0.3–3.4	1	1.6	0.2–13.5	5	0		–	1	9.1	0.7–113

[a] ORs adjusted for age and study.
[b] ORs adjusted for age, study, cumulative exposure to wood dust and leather dust.
[c] ORs also adjusted for cumulative exposure to mineral wools among men.
[d] ORs also adjusted for cumulative exposure to asbestos among men.

adenocarcinoma. As a check for residual confounding, analyses on formaldehyde among men were also adjusted for wood dust exposure by introducing into logistic models the cumulative level of wood dust in five categories, the cumulative level of wood dust as a continuous variable, and the highest lifetime level of wood dust exposure. The results were not markedly changed. Among women the OR for formaldehyde exposure decreased only slightly (OR = 5.8, CI = 1.7–19.4) when adjusted for wood dust exposure (ever/never).

Among men the test of heterogeneity between studies for adenocarcinoma and formaldehyde was significant ($p < 0.01$) and study-specific results were examined. Among men the crude ORs associated with formaldehyde exposure varied considerably, but were above 1 in 9 of the 12 studies (from 1.6 to 54.7). Crude ORs are, however, not meaningful, since other exposures, particularly wood dust, must be taken into account, and the number of cases was in most studies too small to provide adjusted estimates. ORs adjusted for age, study, wood dust, and leather dust exposure were then estimated excluding each study from the analysis consecutively. No important variation was noted: the OR for the highest level of cumulative exposure varied between 2.4 (without Virginia) and 3.2 (without Brescia).

Consistency between studies was difficult to examine among women, given the small number of adenocarcinoma cases in each individual study. There was no statistical evidence of heterogeneity between studies ($p = 0.39$). Exposed cases were observed in four studies, with elevated ORs in three of these (Biella, France, Siena). An OR of 0.8 was observed in the Virginia study (two exposed cases, 24 exposed controls).

Analyses restricted to subjects who had never been exposed to wood or leather dust were also performed (Table 4), even if the small number of cases led to relatively large CIs. Among men the risk of adenocarcinoma increased with the level of exposure to formaldehyde, although the ORs were not statistically significant. A significantly elevated risk was observed among women exposed to the highest level of cumulative exposure.

The distribution of adenocarcinoma cases and control according to exposure to wood dust and formaldehyde is given in Table 5. Only 11 cases exposed to formaldehyde had never been exposed to wood dust. More cases than controls had been exposed to formaldehyde in each category of wood dust exposure. By combining exposure categories it was possible to estimate the ORs associated with exposure to formaldehyde for two levels of wood dust exposure. A non-significantly elevated risk, increasing with the level of exposure to formaldehyde, was observed among those with no or low exposure to wood dust. Higher and significant ORs were observed among those with a moderate or high level of exposure to wood dust. To assess the impact of each study on these results, the joint distribution of exposure to formaldehyde and wood dust was examined after excluding consecutively each individual study. Exclusion of the French study made the largest difference, but a similar pattern was observed: the ORs for the moderate and high level of exposure to formaldehyde for those with no or low exposure to wood dust were respectively 1.2 (CI = 0.4–3.1) and 2.5 (CI = 0.9–7.0). The corresponding ORs for moderate or high level of exposure to wood dust were 8.3 (CI = 2.0–34.0) and 10.2 (CI = 3.0–35.3). Exclusion of the other studies entailed smaller variations.

When the original data of the three studies with an assessment of exposure to formaldehyde were used, for squamous cell carcinoma, no association with exposure to formaldehyde was found. Among men the OR for a

Table 4. Odds ratios of sinonasal adenocarcinoma for cumulative exposure to formaldehyde, among subjects never exposed to wood or leather dust; pooled analysis of 12 case–control studies of sinonasal cancer

Formadehyde	Men				Women			
	No. of controls	No. of cases	OR	95% CI	No. of controls	No. of cases	OR	95% CI
Low	181	1	0.3	0.0–2.3	84	1	0.5	0.1–3.9
Medium	135	4	1.4	0.5–4.3	49	0	0	–
High	71	3	1.9	0.5–6.7	20	5	11.1	3.2–38.0

Table 5. Odds-ratios of sinonasal adenocarcinoma among men for cumulative exposure to formaldehyde, by maximum exposure to wood dust; pooled analysis of 12 case–control studies of sinonasal cancer

Formaldehyde exposure	Controls: wood dust exposure				Adenocarcinoma cases: wood dust exposure				OR (95% CI): wood dust exposure	
	No	Low	Medium	High	No	Low	Medium	High	No or Low	Medium or high
No	1355	45	162	9	38	0	1	0	1 (ref.)	1 (ref.)
Low	190	23	40	12	1	0	1	4		
Medium	139	13	100	14	6	0	6	19	1.3 (0.5–3.3)	7.7 (2.6–22.8)
High	74	1	92	44	4	1	7	79	2.2 (0.8–6.3)	17.0 (6.3–45.6)

Table 6. Odds ratios of adenocarcinoma among men for exposure to formaldehyde, by exposure to wood dust, in two studies (France and the Netherlands) using the original case-by-case evaluation of exposure

Formaldehyde exposure	Wood dust exposure							
	No, possible or low				Probable to medium or high level			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
No	5	314	1	ref.	6	10	1	ref.
Possible or low	4	137	2.0	0.5–7.5	37	27	3.6	1.1–11.9
Probable to medium or high level	1	12	5.0	0.5–48.0	52	15	9.8	2.7–34.8

probable exposure to formaldehyde at medium or high level was 1.3 (CI = 0.7–2.7). The OR for women ever exposed to formaldehyde, estimated from the two studies with female cases (France and Seattle) was 0.7 (CI = 0.2–2.0).

For adenocarcinomas only two studies (France and the Netherlands) could be combined, since only one adenocarcinoma case was included in the Seattle study. The results (Table 6) are consistent with the results of the pooled analysis of the 12 studies using the JEM-based exposure data. Exposure to formaldehyde was associated with elevated risks, for the two levels of wood dust exposure, with higher ORs observed among those exposed to wood dust. Similar results were found in each of the two studies.

Textile dust

The risk of nasal adenocarcinoma was associated with cumulative exposure to textile dust among women only (Table 3). No association with level, probability, or duration of exposure to textile dust was found among men for both histologic types, and among women for squamous cell carcinoma. Among women elevated risks of adenocarcinoma were observed in all categories of probability and duration of exposure, without any clear dose–response relation. Examination of the maximum level of exposure showed that few subjects had been exposed to high levels of textile dust. Among women no case and nine controls had a maximum level greater than 0.5 mg/m^3. Among men three squamous cell carcinomas and nine controls were exposed to more than 0.5 mg/m^3, yielding a significant OR of 6.6 (CI = 1.4–31.8).

The results concerning the increased risk of adenocarcinoma among women were relatively homogeneous across studies (test for heterogeneity: $p = 0.79$). Elevated ORs were observed in the four studies that included more than one case (China, France, Siena, Virginia), and the only case from the Biella study was exposed. Successive exclusion of each study from the analysis did not entail important variations.

When the data of the four studies with a case-by-case evaluation of exposure to textile dust were combined, no association was found between exposure to textile dust and risk of sinonasal cancer among men. Among women non-significant elevated risks were observed for both histologic types, but the OR was higher for adenocarcinoma (OR = 2.3, CI = 0.8–6.3) than for squamous cell carcinoma (OR = 1.5, CI = 0.8–2.9). Exposures to cotton, wool, and synthetics fibers were also examined, but no specific effect of any textile fiber was found.

Asbestos and MMVF

Cumulative exposure to asbestos was associated with an increased risk of squamous cell carcinoma among men. The risk of adenocarcinoma was also non-significantly elevated, but the highest OR was observed for the lowest level of exposure (Table 3).

Men definitely exposed to asbestos (probability > 90%) had an elevated risk of squamous cell carcinoma (OR = 1.9, CI = 0.9–3.9), while for adenocarcinoma the highest OR was observed among men with the lowest probability of exposure (OR = 2.3, CI = 1.5–3.5), with ORs decreasing with increasing probability.

Although the test of heterogeneity between studies was borderline significant ($p = 0.08$), examination of study-specific results for asbestos and squamous cell carcinoma among men did not reveal important discrepancies. The ORs associated with a high level of cumulative exposure to asbestos were above one in nine studies and varied from 1.4 to 7.2. In three studies (Brescia, Germany, and Los Angeles) no association was found. Exclusion of each study from the analysis changed the results only slightly: the ORs for the high level of exposure to asbestos varied from 1.3 (without China) to 1.4 (without Los Angeles).

Exposure to mineral wools was not associated with sinonasal cancer. A significant excess risk of adenocarcinoma was observed among men exposed to a low level of ceramic fibers, but the ORs decreased with the level of cumulative exposure. Among women a significantly increased risk of adenocarcinoma, although based on only three exposed cases, was associated with exposure to continuous filaments. No other significant association was observed between exposure to any type of MMVF and either histologic type.

Silica

Exposure to silica was not associated with nasal cancer among men. Among women a significantly elevated risk of adenocarcinoma was found for the highest level of cumulative exposure, but this result is based on only two exposed cases. A slightly increased risk of squamous cell carcinoma was also observed for a moderate level of cumulative silica exposure, but no case was exposed to the highest level (Table 3).

Adjustment for other occupational exposures, including wood dust, asbestos, and MMVF, did not change the results. There was some indication of a dose–response relationship for adenocarcinoma, since significantly elevated ORs were associated with a high cumulative level (Table 3), a high probability ($OR = 25.1$, $CI = 3.1–202$) and a high maximum level of exposure ($OR = 116$, $CI = 3.5–385$). However, these associations were based on very small numbers, and OR estimates are very imprecise. Most women were exposed to low levels of silica dust, with a low probability. Only three controls and two adenocarcinoma cases were definitely exposed to silica, among them one control and one adenocarcinoma had a maximum level of exposure greater than 0.1 mg/m^3.

Discussion

This pooled analysis was based on a very large dataset for a rare disease such as sinonasal cancer. This increased the power to identify risk factors or to confirm previously suggested associations, and separate analyses by histologic type could be performed. Furthermore, the recoding of occupational histories and the development and use of a JEM allowed us to assess exposure to several substances which were not evaluated in the individual studies.

The pooled analysis suggests that formaldehyde exposure increased the risk of sinonasal adenocarcinoma. There were also some indications of an association with squamous cell carcinoma. Formaldehyde is carcinogenic to animals, and rats exposed by inhalation develop tumors of the nasal cavities. There is also some evidence that occupational exposure to formaldehyde may cause damage in the nasal mucosa [1]. Epidemiologic studies, however, have produced conflicting results. A number of cohort studies of workers exposed to formaldehyde without concomitant exposure to wood dust (*i.e.*, professionals such as embalmers and pathologists as well as industrial workers, in particular in the chemical industry) did not suggest an increased mortality from sinonasal cancer (see ref. 1 for review). It should be stressed, however, that most of these studies were conducted in countries from North America and northern Europe with low background incidence of the neoplasm, resulting in low power to detect a moderate increase in risk. Five case–control studies [18, 19, 25–27], three of them included in this pooled analysis [18, 25, 26], examined the association between formaldehyde exposure and sinonasal cancer. A study in Denmark found non-significant elevated risks for both histologic types, with a higher risk for squamous cell carcinomas [19]. A slightly and non-significant elevated risk of sinonasal cancer of all histologic types was observed in a study in the USA [27]. Among the three studies included in the pooled analysis, two originally reported no association between formaldehyde exposure and squamous cell carcinoma [25, 26], and one found a significant association [18]. In the pooled analysis, for squamous cell carcinoma, no clear relation with cumulative level was noted but elevated risks were observed among men and women probably exposed to formaldehyde. In the studies which examined the risk of adenocarcinoma associated with formaldehyde exposure [18, 19, 26], because of the very strong association between exposure to wood dust and sinonasal adenocarcinoma, it was nearly impossible to assess an independent effect of formaldehyde exposure, since almost all cases exposed to formaldehyde were also exposed to wood dust. This problem was not completely solved in the pooled analysis, since only 18 cases (11 men and seven women) were exposed to formaldehyde and not to wood dust. Residual confounding by wood dust exposure may then not be ruled out. However, several elements add some support to the hypothesis that formaldehyde exposure has an independent effect. A significantly elevated risk was found among women, for whom the problem of confounding by wood dust is minor. Excess risk among men not exposed to wood dust was also suggested, although the results were not statistically significant. The risk associated with formaldehyde exposure seems to be higher among those exposed to wood dust. A similar finding has been previously reported in the study from Olsen and Asnaes [19] (not included in the pooled analysis) and in the French study [26]. Since about half of the adenocarcinoma cases came from the French study, it could be anticipated that the results of the pooled analysis are relatively close to those of the latter. However, the results are reasonably consistent between studies, and a similar pattern was observed after the French study had been excluded from the analysis.

Textile work has been consistently related to sinonasal cancer in several studies within [7, 8, 10, 14] or outside [3, 11–13] this pooled analysis. In some other studies no association was observed [28–30]. Most studies were based on job titles and involved different occupations in the textile industry. Exposure to textile dust and to formaldehyde had been considered as plausible etiological agents. In the pooled analysis the ORs for textile dust were only slightly modified after adjustment for formaldehyde exposure. The association seems to be limited to adenocarcinomas among women, although an increased risk of squamous cell carcinoma was also observed among men exposed to high levels of textile dust. The analysis of the original data of four studies corroborates the results. These findings are also consistent with the high risk of adenocarcinoma among female textile workers and the elevated risk of squamous cell carcinoma for men who had worked as fiber preparers observed in a previous analysis of this dataset [15]. The difference observed between men and women might be explained by exposure to different types of textile fibers. The role of exposure to cotton dust had been previously postulated [10, 31]. The nature of textile fibers was available in four studies, but no specific effect of a particular type of textile was found.

An increased risk of squamous cell carcinoma was observed among men with a high cumulative exposure to asbestos. This association has not been reported previously. In the few case–control studies that evaluated the risk associated with exposure to asbestos, no significant association was found [30, 32], but the level of exposure to asbestos and the histologic type were not taken into account. No consistent suggestion of an increased risk of sinonasal cancer can be derived from the studies of workers exposed to asbestos in mining, asbestos product manufacture, and insulation [33]. However, the expected number of sinonasal cancer deaths in most of these studies was very small, hampering the detection of a small excess risk.

In the present analysis, although the highest ORs were observed for the highest probability and cumulative level of exposure, there was no obvious dose–response pattern with these exposure variables, or with the maximum level or duration of exposure. Exposure to mineral wools was not associated with sinonasal cancer. The number of subjects exposed to other types of MMVF was too small to provide meaningful results.

The association between silica and adenocarcinoma among women was based on small numbers, and may be due to chance. No such association was found among men. An association between silica dust and nasal cancer of all histologic types had been reported in one study [30]. Other occupational exposures of *a-priori* interest (flour dust and coal dust) were not related to the risk of sinonasal cancer in the pooled analysis.

Several limitations should be taken into consideration when interpreting these results. The most important is that occupational exposures were assessed with a JEM, and were based only on job titles, without information about actual working conditions. Misclassification of exposure is then likely to have occurred. However, it can be assumed that subjects reported occupational histories without knowledge of the hypotheses under consideration; therefore assessment of exposures was independent of case/control status. Such non-differential misclassification will in most cases introduce a conservative bias, and is of particular concern for null results. Furthermore, the JEM was developed by experts with extensive experience in assessing these occupational exposures in epidemiologic studies. The fact that the JEM and the original evaluations of exposure, when available, provided similar results also strengthens the reliability of the JEM.

Even with an overall large number of subjects, several analyses were limited by the small number of cases in some subgroups, and no conclusive evidence could be provided on the effect of several exposures. Despite these limitations, this pooled analysis contributed new information on occupational risk factors for sinonasal cancer, and was substantially more informative than the individual participating studies.

In conclusion, results from this pooled analysis are consistent with the hypothesis that occupational exposure to formaldehyde increases the risk of sinonasal cancer, particularly for adenocarcinoma. The results also indicate an elevated risk of adenocarcinoma among women exposed to textile dust, and suggest that exposure to asbestos may increase the risk of squamous cell carcinoma.

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